MEDTRONIC PUERTO RICO OPERATIONS COMPANY

MPROC

STERILIZATION/LABORATORY QUALIFICATION/VALIDATION REPORT AND ROLL-UP DATA

Ethylene Oxide (EO) Dissipation Curve Testing for Bore Plug Accessory Kit Project Report

Revision 1.0

10DEC18

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1. HISTORY AND CONTROL SHEET

REVISION	DATE	DESCRIPTION
1.0	10DEC18	New Release

2. PROTOCOL APPROVAL

Approval:

Giovanni R. Sánchez Cruz	See EQDMS Signature
MPROC Microbiologist / Sterilization	Date
Brenda Simons	See EQDMS Signature
Rice Creek Sr. Microbiologist	Date
Carmen Garcia Diaz	See EQDMS Signature
Sr. Quality Engineer	Date

3. Validation Objectives / Purpose

The purpose of this report is to detail the results of the sterilant residual testing for the Bore Plug Accessory Kit[1] model listed in Table 1. Sterilant residual testing was performed, per plan SSP-128170, using dissipation curves to establish the minimum aeration time required to adequately reduce retained residuals in the Bore Plug Accessory Kit to acceptable levels as per ISO 10993-7:2008/AC:2009 following 1X and 3X sterilization in the 100% EO 75-minute gas dwell Medtronic sterilization process.

4. Scope

The product model covered under the scope of this sterilization qualification is listed below in Table 1.

Table 1 – Product Model Information

DESCRIPTION	MODEL	PIN Number	Material
Bore Plug Accessory Kit	B31060	US PIN: B31060001H PTO PIN: M986033A001	Resin-Polyether Urethane, 55D

The following aspects of the Bore Plug Accessory Kit sterilization are included in this report:

1. EO/ECH Residual
    a) Dissipation Curve
    b) Tolerable Contact Limit (TCL) Determination

The following aspects of the Bore Plug Accessory Kit sterilization validation and microbial testing will be qualified via subsequent studies and are not included in this report:

1. Microbial Performance Qualification (MPQ) – Overkill method
    c) Sub-lethal Cycle ("fractional") – inoculated product/PCD lethality comparison and biological indicator appropriateness ("natural product sterility")
    d) Half Cycle– Inactivation of biological indicator to attain Sterility Assurance Level (SAL) of 10^{-6} or better.
2. Bioburden Estimation
3. Endotoxin Estimation
4. Physical Performance Qualification (PPQ) in the 3M 5XLe Steri-Vac™ 100% EO sterilizer and 3M XL/XLe aerator.

5. Background

Olympus/Percept PC is the next generation primary cell deep brain stimulator (DBS) device. It is planned to be the world's first DBS system capable to deliver closed loop therapy for movement disorders. It is planned to have full body MRI capability at 3T and 1.5T and distance telemetry. It is 10% smaller than predicate product and will attain a 20% longevity improvement. This new product will seek to maintain market share in an increasingly competitive marketplace.

With the introduction of Olympus/Percept PC, a Bore Plug Accessory Kit is intended to be used when an implantable neurostimulator (INS) is implanted with either header ports not connected to an extension.

The Bore Plus Accessory Kit will be sterilized using the 3M Model 5XLe Steri-Vac™ sterilizer within the 100% EO 75-minute gas dwell Medtronic sterilization process.

EO is the most common sterilizing agent used to sterilize medical devices, which are sensitive to heat or irradiation treatment. However, after the sterilization process, residual concentration of EO and Ethylene Chlorohydrin (ECH), might remain in the devices.
These residues are potentially toxic, mutagenic, and carcinogenic substances. Therefore, it is required to remove them from the devices to avoid adverse effects in patients.

[1] Bore Plug Accessory is also known as Connector Plug Kit; it refers to the same kit model B31060.

For reference, the Bore Plug Accessory Kit is shown in its sterile package tray configuration in Figure 1 below and a drawing of the Bore Plug is provided in Figure 2.

Figure 1. Bore Plug Accessory Kit in Sterile Package

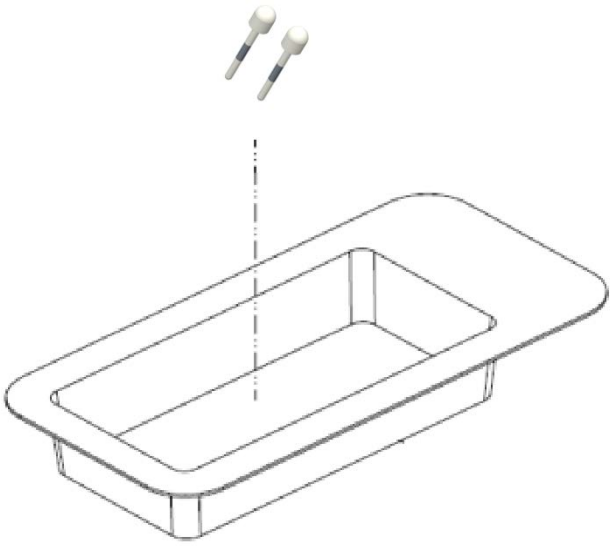


Figure 2. Bore Plug

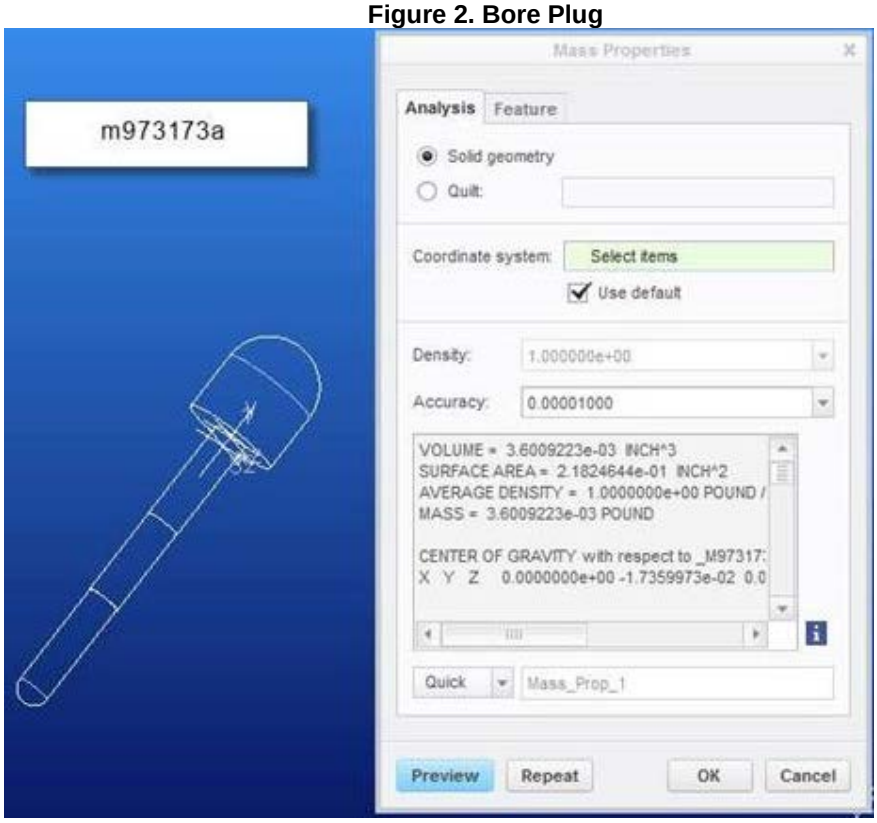


Table 2 – Surface Area for Permanent Patient Contact Components

Component	Surface Area (cm^2)	Patient Contact
Plug - Bore - Over molded	1.41	Permanent
Two (2) Bore Plugs per Tray – Total Surface Area (cm^2)	**2.82**	

Sterilant Residuals:

Sterilant residual testing determines the minimum aeration time required to reduce EO and ECH residuals retained in a sterilized product, to meet the requirements of ISO 10993-7.

Tolerable Contact Limit (TCL):

ISO 10993-7:2008 added the TCL allowable limits (clause 4.3.5) to prevent acute localized tissue irritation resulting from EO or ECH released from the device off-gassing after terminal sterilization with EO. TCL was specifically intended to prevent local irritation by devices with low weight that have high concentrations of residuals.

6. Reference Documents

Table 3 – Reference Documents

Document Number	Document Title	Internal Repository
CRM-0902-0001	Ethylene Oxide Sterilization	Agile
CSS-0401-0015	Sterilization Product Qualification and Maintenance	
10112990DOC	General Requirements for Sterilization Validation	
CSS-0501-XXXX-0007	Product Sterilization Qualification	
DOC000517	Development, Validation, and Requalification of the Product Aeration Process	
CSS-0901-0001-0008	Development, Validation, and Requalification of the 100% EO Sterilization Process	
CSS-0901-0001-0019	Ethylene Oxide Sterilizer System Equipment and Process Equivalence	
CSS-0901-0001-0026	EO Profile Data Roll-Up	
POD_000827	MPROC Neuromodulation Sterilization – 100% EtO	
200023	Medtronic Specification – Sterilization	Enovia
M973173A	Plug – Bore – Overmolded (Drawing)	
EN ISO 10993-7: 2008/ AC: 2009	Biological Evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals	External standard / Guidance
ISO 10993-10:2010	Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization	
EN ISO 11135: 2014	Sterilization of health-care products – Ethylene Oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices	
EN 556-1: 2001 / AC: 2006	Sterilization of medical devices – Requirements for Medical Devices to be designated “Sterile” Part 1: Requirements for terminally sterilized medical devices	
AAMI TIR 28: 2009	Product adoption and process equivalency for ethylene oxide sterilization	
SSP-128170	Ethylene Oxide (EO) Dissipation Curve Testing for Bore Plug Accessory Kit Project Protocol	EQDMS

7. Validation / Qualification Results

A. Definitions

Table 4 – Abbreviations, Acronyms, and Definitions

Term	Term Description
AAMI	Association for the Advancement of Medical Instrumentation
ANSI	American National Standards Institute
CDA	Complete Device Assembly
ECH	Ethylene Chlorohydrin
EN	European Standard (Europäische Norm)
EO	Ethylene Oxide
ISO	International Organization for Standardization
MPROC	Medtronic Puerto Rico Operations Center
NPP	Neuromodulation Policy and Procedures
TCL	Tolerable Contact Limit
Reference CSS-0501-XXXX-0024 for a comprehensive list of sterilization abbreviations, acronyms, and definitions used in this document.	

B. Equipment

The sterilization equipment used is listed in Table 5.

Table 5 – Equipment / Fixturing and Gauging

Description	Identification Number	Calibration Due Date
3M 5XLe Steri-Vac™ sterilizer - The 5XLe system is described as a self-contained, table-top, ethylene oxide sterilizer with internal volume equaling 136 liters/0.136 m^3 (4.8 ft^3) and does not rely on any ancillary equipment to provide heat, steam, or vacuum functions. The internal chamber is made of brushed aluminum with one front mounted door.	5XLe-43 / 54210-564	09OCT18
	5XLe-41 / MR00276	01AUG19
	5XLe-06 / 54210-169	16MAY19
	5XLe-47 / 54210-634	29NOV18
3M XLe Aerator - The XLe aerator is described as a self-contained, table-top aerator with internal volume equaling 150 liters/0.15 m^3 (5.3 ft^3) and does not rely on any ancillary equipment to provide heat. The internal chamber is made of brushed aluminum with one front mounted door.	XLe-43 / 54210-571	09OCT18
	XL-06 / 54210-181	16MAY19
	XL-09 / MR100-682	22DEC18

C. Materials Used

Table 6 – Materials

Description	Part Number	Lot Number	Expiration Date
3M 4-134 EO gas cartridge	168651001	0009304207	30SEP22
		0009249387	30SEP22
		0009366513	31DEC22
Bore Plug Accessory Kit Model B31060	US PIN: B31060001H PTO PIN: M986033A001	N/A	N/A

D. Software Identification

Sterilization software used is listed in Table 7. Software used by Chemical Technologies in EO residual testing is on file at Chemical Technologies Department. Software used by Metrology is on file at Metrology Department.

Table 7 – Software

Software Name	Revision
Eurotherm Review	4.1.323
StAR System	1.0.6

E. Training Assessment

1. MPROC Juncos Sterilization Specialist:
    a) Responsible for developing protocol and report, conduct and/or oversee testing and evaluate test results.
    b) Notify and resolve any discrepancy and/or deviation that may arise during the exercise.
2. MPROC Juncos Quality engineer:
    a) Responsible of reviewing the protocol, report and the data obtained during qualification.
    b) Support discrepancy/deviation investigation, documentation and resolution, as applicable.
3. Medtronic Manufacturing and/or New Product Introduction Engineer:
    a) Build test samples per appropriate procedures.
4. Calibration / Metrology Tech
    a) Responsible for EO sterilizer and aerator profiling and calibration per appropriate procedures.
5. Pace Analytical Laboratory, or other approved EO/ECH residual testing laboratory
    a) Responsible for conducting residual testing of product.

The personnel involved in the execution of this exercise were trained in plan SSP-128170. Training evidence is included in Attachment 1.

F. Sample Size Strategy

Load Configuration

The "D" load configuration consists of:

- Thirty-six (36) universal packages (long tray) were placed at the Top sterilizer wire rack. One hundred and eight (108) accessory kits (small tray) were placed at the Bottom sterilizer wire rack.
    - Six (6) stacks of universal packages are in the Top sterilizer wire rack and twenty-seven (27) stacks of accessory kits in the Bottom sterilizer wire rack.
    - Each stack in the Top sterilizer wire rack has six (6) universal packages as specified in the figure below.
    - Each stack in the Bottom sterilizer wire rack has four (4) accessory kits as specified in the figure above.
    - The Tyvek side of the package is up.

Figure 3 – Configuration "D"

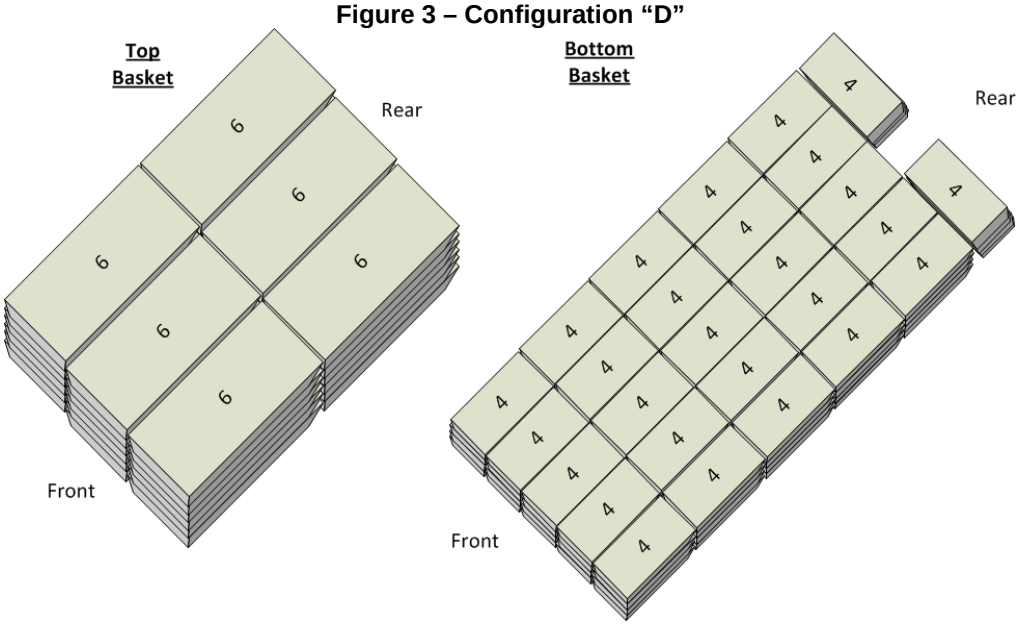


Table 8 - Sample Utilization

Samples Needed	Rationale for Quantity of Samples Required
25	• One (1) sample following 0X sterilization which was reserved as a non-sterilized, manufactured control sample. • Twelve (12) samples following 1X sterilization for EO/ECH residuals test per Table 9 and Table 10. • Twelve (12) samples following 3X sterilization for EO/ECH residuals test per Table 9 and Table 10.

G. Sampling Strategy

The approach chosen for qualifying the sterilant residuals of Bore Plug Accessory Kit was the dissipation curve method. Sterilant residual dissipation curves are constructed from a minimum of three samples per three sterilization lots run at different aeration times to establish the minimum required aeration time. Required aeration time was determined following 1X and 3X sterilization exposures in the 100% EO 75-minute gas dwell Medtronic sterilization process. Samples were tested following 1hrs, 6hrs, 12hrs and 24hrs aeration. Residual test sample types and quantities are detailed in Table 9 below.

Table 9 – Sample Quantities and Sterilization Cycle Requirements

# of Sterilization Exposures	Test Type	Quantity of Test Samples	Rationale for Test Sample Quantity
0X	Residual	1	(1) EO/ECH Control Sample – 0X
1X	Residual	12	(1) samples each for 1hrs, 6hrs 12hrs and 24hrs from three different sterilization lots
3X	Residual	12	(1) samples each for 1hrs, 6hrs, 12hrs and 24hrs from three different sterilization lot combinations

Test samples were built using materials, designs, packaging, and manufacturing processes that mimic the final, finished product intended to be sold. Reject products that mimic the routine product build and have failed product check tests may also were used if the defects/failed check tests were not on patient contacting components. Samples were labeled to designate sample set 1, 2 or 3, sterilization cycle, aeration time and type of testing (i.e. residual or irritation). EO/ECH control sample was labeled accordingly. Refer to Table 10.

Dissipation Curve Sample Set 1 – Run 1:

- A full reference load including sample kits for test, was prepared using Figures 3 and Table 10.
- The entire load was subjected to 75-minutes 100% EO sterilization cycle at MPROC Juncos per POD_000827.
- Immediately following completion of the sterilization cycle, the load was placed into a forced heat aerator (see Table 10 for aeration times). The forced heat aeration timing begins immediately upon placement of samples within the aerator at ambient temperature. The aerator takes 20 to 30 minutes to reach the required temperature set point and simulates “worst-case” conditions for residual dissipation from the product.
- The designated samples were removed and replaced with a dummy at each of the following intervals:
  - Following 1hrs aeration, the #X-a (1hrs) samples are removed.
  - Following 6hrs aeration, the #X-b (6hrs) samples are removed.
  - Following 12hrs aeration, the #X-c (12hrs) samples are removed.
  - Following 24hrs aeration, the #X-d (24hrs) samples are removed.
- All samples were frozen until completion of all sterilization cycles and then all samples were shipped on dry ice to external laboratory for testing.

Upon completion of all sterilization cycles, samples were shipped to Pace Analytical on dry ice for testing.

Table 10 – Sample Distribution per Cycle / Testing Timeline

Samples	Day/Run 1	Day/Run 2	Day/Run 3	Day/Run 4	Day/Run 5
1 Hours Aeration Time	(1) 1X-1a (1) 3X-1a	(1) 1X-2a (1) 3X-1a (1) 3X-2a	(1) 1X-3a (1) 3X-1a (1) 3X-2a (1) 3X-3a	(1) 3X-2a (1) 3X-3a	(1) 3X-3a
6 Hours Aeration Time	(1) 1X-1b (1) 3X-1b	(1) 1X-2b (1) 3X-1b (1) 3X-2b	(1) 1X-3b (1) 3X-1b (1) 3X-2b (1) 3X-3b	(1) 3X-2b (1) 3X-3b	(1) 3X-3b
12 Hours Aeration Time	(1) 1X-1c (1) 3X-1c	(1) 1X-2c (1) 3X-1c (1) 3X-2c	(1) 1X-3c (1) 3X-1c (1) 3X-2c (1) 3X-3c	(1) 3X-2c (1) 3X-3c	(1) 3X-3c
24 Hours Aeration Time	(1) 1X-1d (1) 3X-1d	(1) 1X-2d (1) 3X-1d (1) 3X-2d	(1) 1X-3d (1) 3X-1d (1) 3X-2d (1) 3X-3d	(1) 3X-2d (1) 3X-3d	(1) 3X-3d
Total number of samples in the run	**8**	**12**	**16**	**8**	**4**

Table 11 – EO/ECH Residuals Sterilizer and Aerator Parameters

Parameter	Acceptance Criteria
Conditioning	
Vacuum Rate	7.0 – 13.0 kPa (kilopascals) /minute
Pressure at the beginning of leak check	14.0 - 20.0 kPa
Leak Check Duration	13 – 17 minutes
Leak Check Vacuum Loss	< 4 kPa
Time	30 - 35 minutes
Number of Humidity Pulses	4
Chamber Temperature & Load Probe[1,3]	43.0 – 53.0°C
Chamber Relative Humidity[1,3]	55.0 – 85.0% RH
Pressure, just prior to gas injection	8.0 – 14.0 kPa
Fan Current	0.030 - 0.300 amps (amperes)
EO Exposure	
Gas Inlet Temperature	15.0 – 75.0°C
Exposure Time	72 - 77 minutes
Chamber Temperature[2, 3] (Min/Max)	45.0 – 55.0°C
Chamber Load Temperature[2, 3] (Min/Max)	45.0 – 55.0°C
Gas Concentration[2,3]	>700 mg/L[5]
Gas Weight[2]	127.0±5 grams
Pressure	55.0 – 75.0 kPa
Fan Current	0.030 - 0.300 amps
Post Vacuum	
Vacuum Rate	1.0 - 2.0 kPa/min
Pressure	20.0 - 30.0 kPa
Air Flush	
Time	≥ 25 minutes
Aeration	
Chamber Temperature	44.0 – 56.0°C[6]
Load Temperature	
Time[4]	Aeration time is established in Table 10 of this report.
Fan Current	0.030 - 0.300 amps

[1] Relative humidity and temperature requirements must be met at the end of conditioning
[2] During the first 5 minutes of exposure (directly after completion of the gas injection), temperature and gas concentration spikes or drops may exceed the process parameters while the chamber is equilibrating following gas injection.
[3] Required for Parametric Release
[4] The forced heat aeration timing begins immediately upon placement of samples within the aerator at ambient temperature.
[5] Concentration requirements in the StAR System Sterilization Process Inspection Checklist for 100% ETO is reported as >=500 since is the default for Non-Production cycles. There is no adverse effect on the validation activities as the cycles ran at concentrations higher than 700 mg/L.
[6] Maximum temperature in protocol SSP-128170 was incorrect. Correct maximum temperature is 56.0°C instead of 55.0°C This is a typographical error with no adverse effect on the validation activities as the maximum temperature obtained during the execution of the cycles was 51.2°C

Residual Testing (Total EO and ECH)

The samples were analyzed to evaluate ethylene oxide (EO) and ethylene chlorohydrin (ECH) by gas chromatography utilizing the water extraction method. Testing methodology was conducted in compliance with EN ISO 10993-7:2008.

Table 12 – Extraction conditions for model B31060

Component	MODEL	Exposure Category	Extraction Conditions
Bore Plug	B31060	Permanent	Exhaustive Extraction at 37ºC

H. Acceptance Criteria

Sterilant Residual and TCL Testing

Acceptance Criteria

The upper 95% CI of the mean sterilant residual levels as well as the Tolerable Contact Limit (TCL) obtained from the test model samples must be below the levels stated in Table 13. These requirements must be met following a single or multiple exposure(s) to an EO sterilization process.

Table 13 – Sterilant Residual Requirements

Permanent Exposure Acceptance Criteria:	Total EO:	Total ECH:
Dose for first 24 hours not to exceed	4 mg	9 mg
Dose for first 30 days not to exceed	60 mg	60 mg
Dose for first lifetime not to exceed	2.5 g	10 g
TCL (Or show negligible irritation per ISO 10993-10)	10 µg / cm^2	5 mg / cm^2
Average Daily Dose	0.1 mg/day	0.4 mg/day
Limited Exposure Acceptance Criteria	**Total EO:**	**Total ECH:**
Dose for first 24 hours not to exceed	4 mg	9 mg
TCL (Or show negligible irritation per ISO 10993-10)	10 µg / cm^2	5 mg / cm^2
Average Daily Dose	4 mg/day	9 mg/day

According to ISO 10993-7:2008, a Permanent contact device has the requirement of an average daily dose (M_{add}) of EO to patient shall not exceed 0.1 mg per day. This is calculated using the formulas found in section 4.4.7.2 of the same standard.

Permanent Contact $$M_{add} = \frac{M_d}{25000}$$

Limited Exposure $$M_{add} = M_d$$

Where M_d – is the extract residue in milligrams
25000 – is the number of days per lifetime

Table 14 demonstrates that if you meet the 24-hour, 30 day and lifetime requirements that you will automatically meet the average daily dose requirements as the average daily dose limit is derived from dividing the exposure limit by the number of days in the exposure group i.e. 30 days for prolonged exposure.

Table 14 – Demonstration that ADD limits are met when 24hour, 30 day and lifetime requirements are met

Exposure Acceptance Criteria:	Total EO (mg)	Total ECH (mg)	Average Daily Dose ETO (mg)	Average Daily Dose ECH (mg)
Limited Exposure - Dose for first 24 hours not to exceed	4	9	4	9
Permanent Contact - Dose for lifetime not to exceed	2.5 g	10 g	$\frac{2500mg}{25000days}$ = 0.1 mg/day	$\frac{10000mg}{25000days}$ = 0.4 mg/day

Per ISO 10993-7:2008 Annex G.8.5 Limit based on TCL value
For surface-contacting devices, a TCL-based limit is relevant. The formula for calculation of a mass limit based on the TCL is as follows:

$$m\text{dev, BSC} = \text{TCL} \times A$$

where,
*m*dev, BSC is the allowable residual mass per device, i.e. maximum dose to patient, in milligrams;
TCL is the tolerable contact limit, in milligrams per square centimeter;
A is the surface area of medical device in contact with the body, in square centimeters.

Therefore, for individual devices, the approximate area in square centimeters would be multiplied by the TCL of 10 µg/cm^2 to arrive at the device limit.

EXAMPLE Device surface area in contact with the body = 100 cm^2:

$$m\text{dev, BSC} = 10\ \mu g/cm^2 \times 100\ cm^2 \Rightarrow 1000\ \mu g \Rightarrow 1\ mg$$

Table 15 - TCL Limits for model B31060

Components	Model	Component Surface Area (cm^2)	Total Surface Area (cm^2)	TCL limit (mg)
Bore Plug	B31060	1.41	2.82 (Two bore plugs)	EO – 0.0282 ECH – 14.1

Test Results
Test sample and sterilization information is listed in Table 16. Test results for are summarized from Table 17 to Table 24.

Table 16 – Sterilant Residual Test Sample and Sterilization Information

Pace Work Order	Sterile Lot / Run Number	Sterilization Date	Sample Identification / Test Type
9062599	PR18276431	03OCT18	1X-1a EO/ECH 1X-1b EO/ECH 1X-1c EO/ECH 1X-1d EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH 3X-1d EO/ECH

Pace Work Order	Sterile Lot / Run Number	Sterilization Date	Sample Identification / Test Type
	PR18277432	04OCT18	1X-2a EO/ECH 1X-2b EO/ECH 1X-2c EO/ECH 1X-2d EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH 3X-1d EO/ECH 3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH 3X-2d EO/ECH
	PR18281411	08OCT18	1X-3a EO/ECH 1X-3b EO/ECH 1X-3c EO/ECH 1X-3d EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH 3X-1d EO/ECH 3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH 3X-2d EO/ECH 3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH 3X-3d EO/ECH
	PR18282061	09OCT18	3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH 3X-2d EO/ECH 3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH 3X-3d EO/ECH
	PR18284471	11OCT18	3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH 3X-3d EO/ECH

Table 17 – Sterilant Residual Extraction Information and Results for 0X

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	Results (mg)	
	EO	ECH			EO	ECH
Limited Exposure ***Dose not to exceed for first 24 hours***	4 mg	9 mg	Exhaustive	37°C	Not Detected	
Prolonged Exposure ***Dose not to exceed for first 30 days***	60 mg	60 mg				
Permanent Contact ***Dose not to exceed for lifetime***	2,500 mg	10,000 mg				
Average Daily Dose ***Dose not to exceed for lifetime***	0.1 mg / day	0.4 mg / day				

Table 18 – Sterilant Residual Extraction Information and Results for 1X / 1-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	1X-1a / 1hrs aeration Results (mg)		1X-2a / 1hrs aeration Results (mg)		1X-3a / 1hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure ***Dose not to exceed for first 24 hours***	4 mg	9 mg	Exhaustive	37°C	0.2800	N/D*	0.2578	N/D*	0.2520	N/D*
Prolonged Exposure ***Dose not to exceed for first 30 days***	60 mg	60 mg			0.3088	N/D*	0.2862	N/D*	0.2795	N/D*
Permanent Contact ***Dose not to exceed for lifetime***	2,500 mg	10,000 mg			0.3088	N/D*	0.2862	N/D*	0.2795	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	0.1 mg / day	0.4 mg / day			1.2352 E-05	N/D*	1.1448 E-05	N/D*	1.1180 E-05	N/D*

*N/D = Not detected

Table 19 – Sterilant Residual Extraction Information and Results for 1X / 6-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	1X-1b / 6hrs aeration Results (mg)		1X-2b / 6hrs aeration Results (mg)		1X-3b / 6hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure *Dose not to exceed for first 24 hours*	4 mg	9 mg	Exhaustive	37°C	0.0839	N/D*	0.0760	N/D*	0.0766	N/D*
Prolonged Exposure *Dose not to exceed for first 30 days*	60 mg	60 mg			0.1013	N/D*	0.0925	N/D*	0.0937	N/D*
Permanent Contact *Dose not to exceed for lifetime*	2,500 mg	10,000 mg			0.1013	N/D*	0.0925	N/D*	0.0937	N/D*
Average Daily Dose *Dose not to exceed for lifetime*	0.1 mg / day	0.4 mg / day			4.052 E-06	N/D*	3.700 E-06	N/D*	3.748 E-06	N/D*

*N/D = Not detected

Table 20 – Sterilant Residual Extraction Information and Results for 1X / 12-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	1X-1c / 12hrs aeration Results (mg)		1X-2c / 12hrs aeration Results (mg)		1X-3c / 12hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure *Dose not to exceed for first 24 hours*	4 mg	9 mg	Exhaustive	37°C	0.0328	N/D*	0.0298	N/D*	0.0329	N/D*
Prolonged Exposure *Dose not to exceed for first 30 days*	60 mg	60 mg			0.0328	N/D*	0.0298	N/D*	0.0329	N/D*
Permanent Contact *Dose not to exceed for lifetime*	2,500 mg	10,000 mg			0.0328	N/D*	0.0298	N/D*	0.0329	N/D*
Average Daily Dose *Dose not to exceed for lifetime*	0.1 mg / day	0.4 mg / day			1.312 E-06	N/D*	1.192 E-06	N/D*	1.316 E-06	N/D*

*N/D = Not detected

Table 21 – Sterilant Residual Extraction Information and Results for 1X / 24-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	1X-1d / 24hrs aeration Results (mg)		1X-2d / 24hrs aeration Results (mg)		1X-3d / 24hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure ***Dose not to exceed for first 24 hours***	**4 mg**	**9 mg**	**Exhaustive**	**37°C**	0.0094	N/D*	0.0075	N/D*	0.0094	N/D*
Prolonged Exposure ***Dose not to exceed for first 30 days***	**60 mg**	**60 mg**			0.0094	N/D*	0.0075	N/D*	0.0094	N/D*
Permanent Contact ***Dose not to exceed for lifetime***	**2,500 mg**	**10,000 mg**			0.0094	N/D*	0.0075	N/D*	0.0094	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**			3.76 E-07	N/D*	3.0 E-07	N/D*	3.76 E-07	N/D*

*N/D = Not detected

Table 22 – Sterilant Residual Extraction Information and Results for 3X / 1-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	3X-1a / 1hrs aeration Results (mg)		3X-2a / 1hrs aeration Results (mg)		3X-3a / 1hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure ***Dose not to exceed for first 24 hours***	**4 mg**	**9 mg**	**Exhaustive**	**37°C**	0.3714	N/D*	0.3651	N/D*	0.3768	N/D*
Prolonged Exposure ***Dose not to exceed for first 30 days***	**60 mg**	**60 mg**			0.4677	N/D*	0.4583	N/D*	0.4711	N/D*
Permanent Contact ***Dose not to exceed for lifetime***	**2,500 mg**	**10,000 mg**			0.4677	N/D*	0.4583	N/D*	0.4711	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**			1.8708 E-05	N/D*	1.8332 E-05	N/D*	1.8844 E-05	N/D*

*N/D = Not detected

Table 23 – Sterilant Residual Extraction Information and Results for 3X / 6-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	3X-1b / 6hrs aeration Results (mg)		3X-2b / 6hrs aeration Results (mg)		3X-3b / 6hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure *Dose not to exceed for first 24 hours*	4 mg	9 mg	Exhaustive	37°C	0.1171	N/D*	0.1137	N/D*	0.1211	N/D*
Prolonged Exposure *Dose not to exceed for first 30 days*	60 mg	60 mg			0.1536	N/D*	0.1489	N/D*	0.1595	N/D*
Permanent Contact *Dose not to exceed for lifetime*	2,500 mg	10,000 mg			0.1536	N/D*	0.1489	N/D*	0.1595	N/D*
Average Daily Dose *Dose not to exceed for lifetime*	0.1 mg / day	0.4 mg / day			6.144 E-06	N/D*	5.956 E-06	N/D*	6.380 E-06	N/D*

*N/D = Not detected

Table 24 – Sterilant Residual Extraction Information and Results for 3X / 12-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	3X-1c / 12hrs aeration Results (mg)		3X-2c / 12hrs aeration Results (mg)		3X-3c / 12hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure *Dose not to exceed for first 24 hours*	4 mg	9 mg	Exhaustive	37°C	0.0477	N/D*	0.0478	N/D*	0.0491	N/D*
Prolonged Exposure *Dose not to exceed for first 30 days*	60 mg	60 mg			0.0667	N/D*	0.0663	N/D*	0.0692	N/D*
Permanent Contact *Dose not to exceed for lifetime*	2,500 mg	10,000 mg			0.0667	N/D*	0.0663	N/D*	0.0692	N/D*
Average Daily Dose *Dose not to exceed for lifetime*	0.1 mg / day	0.4 mg / day			2.668 E-06	N/D*	2.652 E-06	N/D*	2.768 E-06	N/D*

*N/D = Not detected

Table 25 – Sterilant Residual Extraction Information and Results for 3X / 24-hour aeration

Device Exposure Category and Requirement Description	Acceptance Criteria		Extraction Method	Extraction Condition	3X-1d / 24hrs aeration Results (mg)		3X-2d / 24hrs aeration Results (mg)		3X-3d / 24hrs aeration Results (mg)	
	EO	ECH			EO	ECH	EO	ECH	EO	ECH
Limited Exposure *Dose not to exceed for first 24 hours*	4 mg	9 mg	Exhaustive	37°C	0.0121	N/D*	0.0118	N/D*	0.0126	N/D*
Prolonged Exposure *Dose not to exceed for first 30 days*	60 mg	60 mg			0.0121	N/D*	0.0118	N/D*	0.0126	N/D*
Permanent Contact *Dose not to exceed for lifetime*	2,500 mg	10,000 mg			0.0121	N/D*	0.0118	N/D*	0.0126	N/D*
Average Daily Dose *Dose not to exceed for lifetime*	0.1 mg / day	0.4 mg / day			4.84 E-07	N/D*	4.72 E-07	N/D*	5.04 E-07	N/D*

*N/D = Not detected

Table 26 – EO TCL Results for 1X / 1-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1a / 1hrs aeration Results (mg)	1X-2a / 1hrs aeration Results (mg)	1X-3a / 1hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 1-hour heated aeration	2.82	0.0282	0.3088	0.2862	0.2795
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 27 – EO TCL Results for 1X / 6-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1b / 6hrs aeration Results (mg)	1X-2b / 6hrs aeration Results (mg)	1X-3b / 6hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 6-hour heated aeration	2.82	0.0282	0.1013	0.0925	0.0937
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 28 – EO TCL Results for 1X / 12-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1c / 12hrs aeration Results (mg)	1X-2c / 12hrs aeration Results (mg)	1X-3c / 12hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 12-hour heated aeration	2.82	0.0282	0.0328	0.0298	0.0329
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 29 – EO TCL Results for 1X / 24-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1d / 24hrs aeration Results (mg)	1X-2d / 24hrs aeration Results (mg)	1X-3d / 24hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 24-hour heated aeration	2.82	0.0282	0.0094	0.0075	0.0094
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 30 – EO TCL Results for 3X / 1-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1a / 1hrs aeration Results (mg)	3X-2a / 1hrs aeration Results (mg)	3X-3a / 1hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 1-hour heated aeration	2.82	0.0282	0.4677	0.4583	0.4711
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 31 – EO TCL Results for 3X / 6-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1b / 6hrs aeration Results (mg)	3X-2b / 6hrs aeration Results (mg)	3X-3b / 6hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 6-hour heated aeration	2.82	0.0282	0.1536	0.1489	0.1595
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 32 – EO TCL Results for 3X / 12-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1c / 12hrs aeration Results (mg)	3X-2c / 12hrs aeration Results (mg)	3X-3c / 12hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 12-hour heated aeration	2.82	0.0282	0.0667	0.0663	0.0692
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Table 33 – EO TCL Results for 3X / 24-hour aeration

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1d / 24hrs aeration Results (mg)	3X-2d / 24hrs aeration Results (mg)	3X-3d / 24hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 24-hour heated aeration	2.82	0.0282	0.0121	0.0118	0.0126
ECH	Not to exceed 5 mg/cm^2			14.1	N/D*	N/D*	N/D*

*N/D = Not detected

Per ISO 10993-7:2008, dissipation curves are used to estimate the post-sterilization time required for products to reach residue limits, principally for EO. Dissipation of EO from most materials and devices follows first-order kinetics. A plot of the natural logarithm of the experimentally determined EO concentration against time after sterilization is linear. Release shall then be based on the time after sterilization when the mean regression line intersects the maximum allowable residue.

Regression analysis of pooled data from three lots established the nature of the dissipation curve, enabling the model device to be released at the calculated upper 95% prediction limit for it., *L*p, for the allowed residue limit for the product.

The ISO 10993-7:2008 Residual Regression Equation is as follow:

$$L_p = x_o + t_\alpha \times \sqrt{\frac{(S_\alpha)^2}{b^2} \times \left[1 + \frac{1}{n} + \frac{(y_o - y_\mu)^2}{b^2 \times \sum (x_i - x_\mu)^2}\right]} \qquad x_o = \frac{y_o - a}{b}$$

where
x_o is the calculated average value of the release time corresponding to the EO limit;
y_o is the logarithmic value of the EO limit;
a is the intercept of the linear regression line obtained from the plot ln[EO] α time;
b is the slope of the regression line;
L_p is the prediction limit for a single individual of the product;
$t\,\alpha$ is the student t value at significance α with $n - 2$ degrees of freedom;
$(S\,\alpha)2$ is the residual variance of the regression line;
y_μ is the average of logarithmic EO values;
n is the number of values;
x_i is the individual time after sterilization at which measurements are made;
x_μ is the average of the times after sterilization;
$\Sigma\ (x_i - x_\mu)2$ is the sum of squares for x (time).

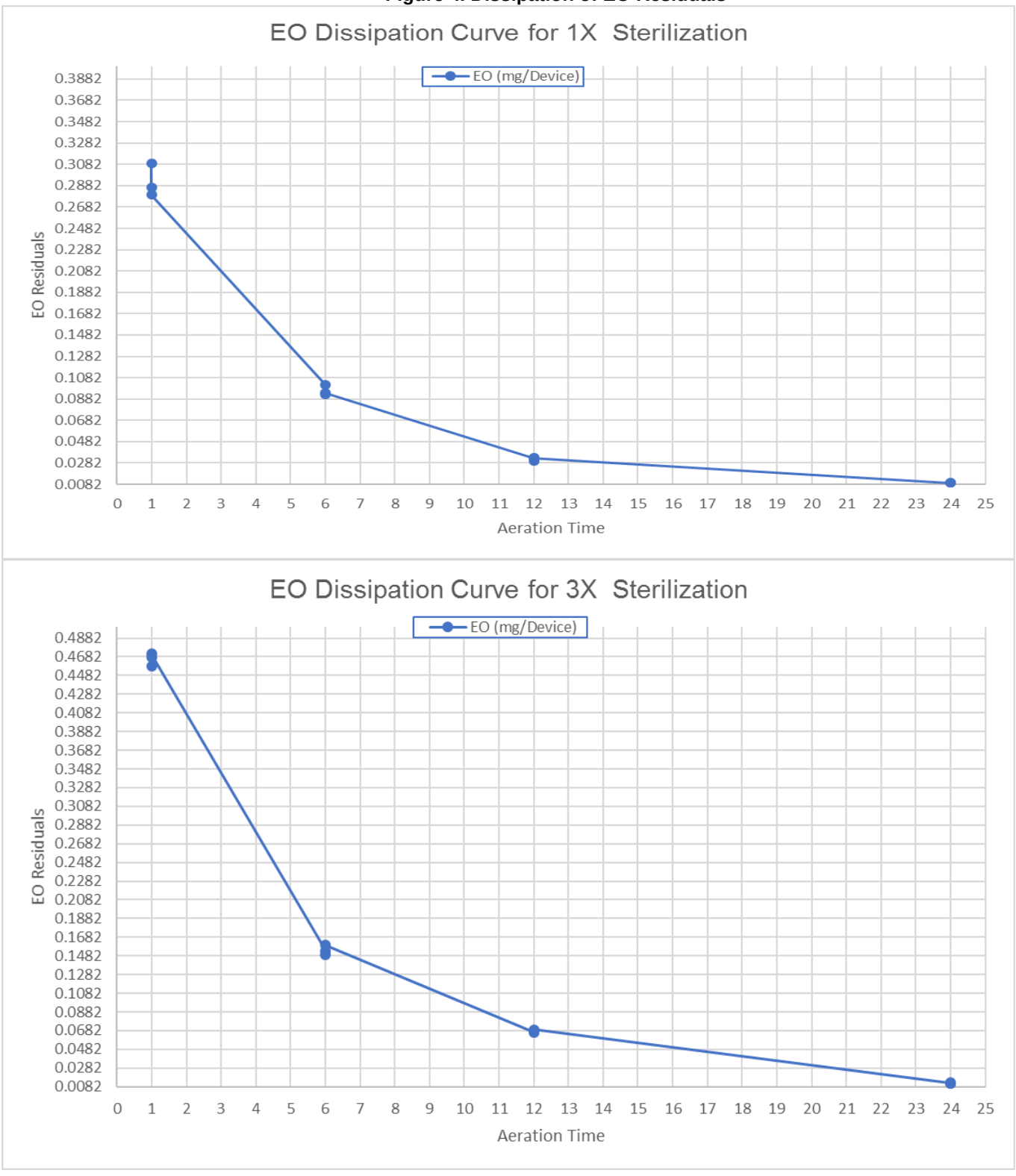
For Bore Plug Accessory Kit, three sterilization cycles were performed for each sample point. A total of 25 units of were analyzed.

Right after one hour of forced aeration, the samples showed a highest initial concentration of 0.3088 mg/device of EO residual level for 1X sterilization (Table 18) and 0.4711 mg/device of EO residual level for 3X sterilization (Table 22), what means that these values are lower than the established limits of 4mg/device.

Test results are documented in Tables 17 through Table 33. Based on these summarized results the EO and ECH residuals requirements are met as soon as 1 hour of forced aeration. Nevertheless, based on the 95% Prediction Limit calculation, included in Attachment 10, to reach the limits of EO that meet the TCL requirements, a total of 18.28 hours is required after 1X sterilization and 19.89 hours are required after 2X and 3X sterilization.
Therefore, the total hours of forced aeration required to reach ISO Limit within a 95% Prediction Limit are 19 hours after 1X sterilization and 20 hours after 2X and3X sterilization. After this period, the values of 0.0282 mg/device of EO residual were reached. Refer to Attachment #10 and Figure 4.

The residual levels of ECH did not exceed the maximum limits established since the first sample was analyzed.

Figure 4. Dissipation of EO Residuals



8. Protocol Deviations

No deviation was created as part of the validation activities

9. Re-qualification Requirements

An assessment will be conducted annually (per DOC000517) to determine if sterilant residual testing is required.

10. Conclusion

The minimum periods of forced heat aeration following sterilization exposure for the product model in the scope of this qualification are described below in Table 34. The maximum aeration allowed is 26 hours of forced heat aeration following each sterilization exposure.

Table 34 – Minimum Aeration Times

Model	1X Aeration (hours)	2X / 3X Aeration(hours)
B31060	19	20

11. Attachments

Attachment #1 – Training Attendance Sheet

Attachment #2 – PR18276431 Data and Chart

Attachment #3 – PR18277432 Data and Chart

Attachment #4 – PR18281411 Data and Chart

Attachment #5 – PR18282061 Data and Chart

Attachment #6 – PR18284471 Data and Chart

Attachment #7 – EO and ECH Laboratory Data Package

Attachment #8 – EO and ECH Final Report and Summary Sheets

Attachment #9 – Ethylene Oxide Residual Freezer Samples Logs

Attachment #10 – EO Residual 95% Calculator

Attachment #11 – Software Validation Report for EO Residual 95% ISO Calculator FT132421 Rev. A